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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/382,088	08/24/1999	ERNEST G. HOPE	HOPEP001	4793

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/382,088	HOPE ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51,66 and 294-313* is/are pending in the application.

4a) Of the above claim(s) *294,295,298-304 and 308-311* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51,66,296,297,305-307,312,and 313* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed 1/10/08 have been entered.

2. Claims 51, 66, and 294-313 are pending.

In the election filed 12/05/07 Applicant elected the species of SEQ ID NO:6 without traverse. Accordingly, the claims are only under examination as they read on the polypeptide of SEQ ID NO:6. Note that Claim 66 is under examination because the polypeptide of SEQ ID NO:6 can be considered to "consist essentially of" SEQ ID NO:3, but Claim 298 is not under examination because the polypeptide of SEQ ID NO:6 cannot be considered to "consist of" SEQ ID NO:3.

Claims 294-295, 298-304, and 308-311 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claims 51, 66, 296-297, 305-307, and 312-313 are under examination.

3. The specification stands objected to for the following informalities:

A) The disclosure is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code. See, for example, page 13 of the specification. Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable code. See MPEP 608.01.

4. In view of the instant amendments, the previous rejections under the second paragraph of 35 U.S.C. 112, and the first paragraph of 35 U.S.C. 112 (for the introduction of new matter into the claims), have been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 51, 66, 296-297, 305-307, and 312-313 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification is not enabled for the claimed method employing peptides or polypeptides other than those consisting of SEQ ID NOS:3 and 6 for a method of reducing NK cell-induced vascular leak syndrome.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

In the submission of a specification Applicant has many choices. Applicant can either submit a thorough discussion of the claimed invention or Applicant can submit just a minimal description of the invention itself. In choosing to disclose as little as possible, Applicant does, however, face the possibility that the invention might be limited to only that which has been disclosed, i.e., Applicant has sacrificed possible breadth. In the instant case, Applicant has chosen to provide only a minimal disclosure. Applicant has chosen not to disclose the mechanism by which the claimed method might function and Applicant has further chosen not to disclose how the specific degenerate peptides employed in the specification were arrived at. While a vague mention of "shared homology" between huHSP47 and HLA-A2 is disclosed in Example 8, there is no disclosure of the relevance of said shared homology to the method of the instant claims. Regardless, it is noted that the protective effect of the claimed method is disclosed as being non-MHC restricted.

The only actual support for the claimed method offered in the instant specification is the part of Example 3 spanning pages 54 and 55. HuHSP47 (SEQ ID NO:6) and a fragment of the protein (SEQ ID NO:3) are shown to protect EC from CIK-mediated lysis. Note that the specification fails to even disclose how the fragment of SEQ ID NO:3 was arrived at. The specification does show, however, that some fragments of SEQ ID NO:6, e.g., fragments *comprising* SEQ ID NO:3, do *not*

function in the claimed method (deletion mutant 2) presumably because of "altered conformation".

As set forth previously, the specification fails to provide guidance as to how to use a composition comprising any immunoprotecting variant or fragment of the polypeptide comprising the amino acid sequence of SEQ ID NO:6 or SEQ ID NO:3. Predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acids in the sequence, if any, are tolerant of modification and which are conserved or less tolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its functional usefulness, as evidenced by the teachings of Abaza et al. (1992, of record). Abaza et al. teach that even a single amino acid difference in an antigen may effect antibody binding by teaching that an amino acid substitution of myoglobin outside the epitope recognized by a monoclonal antibody causes the myoglobin to be unreactive with said antibody. Therefore, predicting which polypeptides, fragments, variations and modifications of HSP47, would retain the desired immunoprotective characteristics and therefore will be useful in a method for reducing immune mediated damage is complex and well outside the realm of routine experimentation.

Accordingly, there is no way to determine which of the variant proteins and peptides encompassed for use in the method of the instant claims might function in an effective treatment and which might not.

Applicant's arguments, filed 5/10/07, have been fully considered but they are not persuasive. Applicant argues that little experimentation would be necessary and that it is known in the art how to make polypeptide sequence substitutions.

While the art may recognize how to make substituted polypeptide sequences, the art does not recognize how substituted polypeptides *that would function in the claimed method* would be made. At best, a method of trial and error might be employed. Given that said methods comprise no particular expectation of success with any particular test candidate, said methods are not enabled unless the test pool is limited. In the instant case, no guidance has been provided as to which amino acids might be substituted and which might not, thus all possibilities must be tested. Indeed, the claims would even encompass the use of variants of SEQ ID NO:6 in which the sequence of SEQ ID NO:3 had been completely eliminated by substitution. Given claims drawn to the use of SEQ ID NO:6 variants with as little as 80% identity, proteins comprising 1 to 80+ substitutions, additions, and/or deletions, each substitution, addition, and/or deletion comprising one of 20 possible amino acids, i.e., an essentially countless number of variants, are encompassed for use in the method of the instant claims. The testing of an essentially countless number of variants cannot be considered to be routine experimentation.

The claims now encompass the reducing or preventing of any disease in which lymphocytes and NK or NK-like cells cause "immune-mediated damage". First, the prevention of a disease comprises a significantly higher enablement issue, requiring a significantly higher showing of enablement, than does the treatment (or reducing) of a disease. A review of the specification shows no prevention of any disease. For this reason alone the claims are not enabled. Also note that lymphocytes (of which NK cells are a species) are involved in

numerous unrelated diseases that comprise immune-mediated damage. Consider, for example, multiple myeloma versus graft versus host disease. There is absolutely no evidence of record that these very different diseases could be treated (either prevented or reduced) by the claimed method. A claim to a single effective prevention and treatment for such unrelated diseases can be referred to as the discovery of the medical "silver bullet" and flies in the face of scientific reality.

A review of the specification also reveals that "HSP47 polypeptide" is defined at page 10 as having as little as 70% sequence identity with an HSP47. All possible deletions, additions, mutations, etc. (limited only by the 70% identity requirement) are encompassed by the term. Accordingly the HSP47 employed in the method of Claims 305, 306, 312, and 313 comprises countless variations, none of which have been demonstrated to function in the claimed method.

Applicant's arguments, filed 1/10/08, have been fully considered but they are not persuasive. Applicant argues that in reciting the phrase "consisting essentially of" the polypeptides employed in the instant claims the claimed method is enabled.

See the Examiner's position regarding reducing and preventing all immune-mediated damage above.

Regarding specifically how the SEQ ID NO:3 fragment of SEQ ID NO:6 was arrived at and discovered to be immunoprotecting in certain applications, Applicant argues that "the specification discloses that this sequence corresponded to the HLA-A2 homology region, which was present in the deletion 3, which was the smallest deletion mutant disclosed."

This is an example of the minimal disclosure which is referenced in the body of the rejection above. What precisely about HLA-A2 homology offers any sort of immunoprotection? What about this sequence invited investigation? Absent any of this sort of teaching it is unclear how any variations on the sequence of SEQ ID NO:6, and it's fragment SEQ ID NO:3, can be enabled by the instant specification.

Regarding the argument that the polypeptide of Claim 312 (presumably Applicant meant Claim 313) comprises no more than a deviation of 20 amino acids, said deviation still comprises an essentially limitless number of possibilities. Consider that

the polypeptide encompasses from 1-20 deletions, mutations, additions, etc, at every possible location, and every possible combination of locations, in the 417 amino acid polypeptide, and then consider that every mutation or addition comprises 20 possibilities. Thus, it is unclear that it could even be established how many possible muteins are encompassed for use in the method of the claim.

7. Claims 51, 66, 296-297, 305-307, and 312-313 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

As set forth previously, there is insufficient written description to show that Applicant was in possession of a sequence *comprising* SEQ ID NO:6 or SEQ ID NO:3, or 80%, 90%, or 95% variants thereof, effective to prevent damage of cells, tissues, or organs by lymphocytes, NK cells, or NK-like cells. As set forth above, it is clear that the claims encompass the use of an essentially unlimited genus of variant proteins and peptides, none of which have been disclosed. As set forth in *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 and reiterated in University of *Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1892, "A description of what a material does, rather than what it is, usually does not suffice". In the instant case the proteins and peptides are described by function only, no meaningful structural characteristics are disclosed. Thus, an adequate written description of the claimed genus has not been disclosed. Accordingly, one of skill in the art would conclude that the specification fails to disclose either common functional *and* structural features, or a representative number of species, to describe the claimed genus of proteins and peptides encompassed for use in the method of the instant claims.

Note that given the breadth of the immune-mediated diseases encompassed for treatment by the claimed method, and that the method now includes the prevention of all such diseases, it is unclear that Applicant was in possession of *any* polypeptide capable of being used in the method of the instant claims.

Applicant's arguments, filed 1/10/08, have been fully considered but they are not persuasive. Applicant cites pages of case law in support of the claimed method.

A review of cited case law reveals no examples of a finding wherein an adequate written description requires *no* representative examples of the claimed invention. Note that, as set forth above, in this instance there is no evidence that even the polypeptide of SEQ ID NO:6, nor its fragment SEQ ID NO:3, would function to reduce or prevent all immune-mediated damage caused by lymphocytes. Thus, *no* examples of any polypeptide meeting the limitations of the claims are disclosed.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 51, 66, 305-307, and 312-313 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hoppe et al. (1995, IDS).

As set forth previously, Hoppe et al. teaches a method for reducing immune-mediated damage to cells, tissues or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of polypeptide comprising Hsp47 which comprises the amino acid sequence AVLSAEQLR (SEQ ID NO:3), or SEQ ID NO:6, which encompasses the claimed variants thereof and a sequence which hybridizes with a nucleic acid sequence of SEQ ID NO:4, wherein the immune-mediated damage is caused by CIK cells. The reference further teaches the purification of the protein and its use in reducing immune-mediated damage caused by lymphocytes (vascular leak syndrome) (see particularly the last line of the abstract).

Applicant's arguments, filed 1/10/08, have been fully considered but they are not persuasive. Applicant argues that the newly claimed limitation that the HSP47 polypeptide "is free of at least one component naturally occurring with HSP47" separates the claimed method from the method of the reference.

Applicant further argues a lack of expectation of success. Applicant argues that the reference does not teach a contacting step.

As the HSP47 of the reference was administered to a SCID/hu *in vivo* model, it is clear that the polypeptide was "free of at least one component naturally occurring with HSP47". Just as clearly, to be used in the model the polypeptide had to be contacted with at least a cell, tissue, or organ. Note that the reference does not teach that the method "will" be investigated but rather that the method "is currently under investigation". Regardless, the fact that the claimed method would be readily envisaged by the reference would allow for a rejection for anticipation. Regarding a lack of expectation of success, the reference clearly teaches that the polypeptide offers protection of HUVEC cells against cytolysis, thus, the ordinarily skilled artisan would have had every expectation of success. Further, it is unclear why Applicant would make this argument given that the instant specification offers no more than an *in vitro* model to enable the claimed method.

11. The following are new grounds for rejection.

12. Claims 6251, 66, 296-297, 305-307, and 312-313 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method for preventing immune-mediated damage (Claims 51 and 305).

B) A method employing multiple copies of the polypeptide (Claim 296).

C) A method employing two copies of the amino acid sequence (Claim 297).

Regarding A), Applicant cites previously pending Claim 60 in support of the limitation.

Claim 60 was not an original claim. The claim was

submitted in the amendment of 10/31/03. It is noted that at that time no support from the limitation was cited and at this time none has been found.

Regarding B) and C), no support has been cited and none has been found

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

15. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see www.uspto.gov/ebc/newusers.html. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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